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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/515,513 | 02/29/00 | LI W | 0942.4870001 |

HM22/0907

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| **ART UNIT** | **PAPER NUMBER** |
| 1656 | 6 |

**DATE MAILED:** 09/07/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/515,513 | Applicant(s) LI ET AL. | |
|---|---|---|---|
| | Examiner Janell E. Taylor | Art Unit 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☒ Responsive to communication(s) filed on *21 June 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

## DETAILED ACTION

### *Election/Restrictions*

1. Claims 31 and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in a telephone conversation with Ann Summerfield on August 14, 2000.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a reverse transcriptase molecule, does not reasonably provide enablement for *any* composition for making an increased amount or percentage of full length cDNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In Ex parte Forman, 230 USPQ 546 (Bd. App. 1986), the Board considered the issue of enablement in molecular biology. In considering these factors: (a) in order to practice the invention, the practitioner must be able to use any composition for making an increased amount or percentage of full length cDNA; (b) the specification provides guidance only for reverse transcriptase as a way of making full length DNA; (c) working

examples are presented only as directed to RT; (d) the invention is directed to any composition; (e) the prior art teaches reverse transcriptase or other polymerases suitable for synthesizing cDNA; (f) the level of skill in molecular biology is high; (g) the results of experiments involving any composition is not predictable; (h) the claims are broadly drawn, reciting any possible composition. Based on the above analysis, one of ordinary skill in the art would be subject to undue experimentation in using a composition to increase the amount or percentage of full-length cDNA.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. The term "elevated" in claim 5 is a relative term, which renders the claim indefinite. The term "elevated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Furthermore, there is no comparison of the term “elevated”, in other words, elevated relative to what.

5. The term "lowering" in claim 7 is a relative term, which renders the claim indefinite. The term "lowering" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

6. The term "increasing" in claim 13 is a relative term which renders the claim indefinite. The term "increasing" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the

art would not be reasonably apprised of the scope of the invention. Furthermore, there is no teaching of what the length is increasing in relation to.

7. The term "increases the amount" in claim 16 is a relative term which renders the claim indefinite. The term "increases the amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

8. The term "increased amount" in claims 29 and 30 is a relative term which renders the claim indefinite. The term "increased amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

9. Claims 18 and 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to the method of claim 18, wherein conditions prevent, inhibit, reduce, or substantially reduce digestion of mRNA in the double stranded mRNA/cDNA hybrid. However, it is not clear what the Applicant intends by this claim because claim 18, from which is depends, is drawn to conditions which allow digestion of a single stranded mRNA contained in the mRNA/cDNA hybrids formed. However, if the mRNA of claim 18 is single stranded, how is it possible that it is in the mRNA/cDNA hybrid? Clarification is required.

***Claim Rejections - 35 USC § 102***

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-6, 15-16, and 21-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Sloma (US Patent 4,748,233).

Claim 1 is drawn to a method for synthesizing one or more cDNA molecules or population of cDNA molecules comprising: mixing at least one mRNA or poly A RNA template or population of such templates with at least one polypeptide having reverse transcriptase activity; and incubating said mixture under conditions sufficient to increase the amount of percentage of full-length cDNA molecules synthesized. Claim 2 is drawn to the conditions reducing internal priming. Claim 3 is drawn to the polypeptide being a reverse transcriptase which is selected from the group consisting of M-MLV RT, RSV RT, AMV RT, MAV RT, and HIV RT, and derivatives and fragments thereof. Claim 4 is drawn to the reverse transcriptase having reduced RNase H activity. Claim 5 is drawn to the primers hybridizing at elevated temperatures. Claim 6 states that those temperatures are between 20 and 90 degrees C. Claim 15 is drawn to the method of claim 1, wherein at least one cDNA molecule is hybridized under conditions sufficient to make at least one second nucleic acid molecule complementary to all or a portion of said at least one cDNA molecule, thereby producing one or more double stranded cDNA molecules. Claim 16 is drawn to the method of claim 15, wherein the conditions

for making said second molecule increases the amount or percentage of full-length double stranded cDNA molecules. Claims 21 and 22 are drawn to a cDNA molecule made by the method of claims 1 and 15, respectively. Claims 22-28 are drawn to vectors and host cells containing the nucleic acid molecules. Claim 29 is drawn to a kit for making full length cDNA molecules comprising at least one component selected from the group consisting of one or more primers, one or more RT inhibitors, one or more RT enzymes, one or more nucleotides, one or more cap structures, or one of more RT buffers, and instructions. Claim 30 is drawn to a composition for making an increased amount or percentage of full-length cDNA.

Sloma teaches "Synthesis of cDNA employs avian myeloblastosis virus reverse transcriptase. This enzyme catalyzes the synthesis of a single strand of DNA from deoxynucleoside triphosphates on the mRNA template. The poly r(A) tail of mRNA permits oligo (dT) ...to be used as a primer for cDNA synthesis...cDNA synthesis is generally conducted by combining the mRNA, the dNTPs, the oligo (dT) and the reverse transcriptase in a properly buffered solution.... This solution is incubated at an elevated temperature of about 40-50 degrees C, for a time sufficient to allow formation of the cDNA copy...(Col. 4, lines 16-37). Therefore, Sloma teaches synthesis of a cDNA molecule, in the presence of an RT such as AMV, which is known to not possess RNase H properties, at an elevated temperature.

Sloma goes on to teach "Synthesis of [a] complementary cDNA strand is conducted under essentially the same conditions as the synthesis of the cDNA copy..." (Col. 4, liens 57-63).

Sloma also teach the cDNA molecule of the above method may be "inserted into a suitable cloning vector, which is used for transforming appropriate host cells." (Col. 5, lines 20-23). Sloma also teach the components of the kit of claim 29 in examples 1 and 2. Sloma also teaches reverse transcriptase, which is a composition for making an increased amount of full length cDNA.

***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sloma as applied to claims 1-6, 15-16, and 21-30 above, and further in view of Copeland et al. (US Patent 6,103,473).

Claims 7 and 8 depend from claim 2 but recite the further limitation that the amount of primer is lowered relative to the amount of template, and the ratio is lowered from about 5:1 to about 1:20.

Sloma does not teach primer: template ratios.

Copeland et al. teaches that the primer: template ratio is in a ratio of 1:1 in regards to the synthesis of DNA. (Col. 21-22, lines 65-4).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Sloma with that of Copeland. This is because it was well known in the art at the time of the invention that a variety of template: primer ratios

were useable in different circumstances, depending upon the needs of that given reaction. It was also well known that lowering the primer to template ratio would have caused synthesis to proceed at a slower rate, which would have been beneficial in many applications such as cDNA synthesis. Although the exact primer: template ratio of claim 8 is not taught, it would have been obvious to one of ordinary skill in the art to vary this ratio in order to obtain the optimal results. It would not have been undue experimentation on the part of the practitioner to vary this ratio until the maximal amount of cDNA product, at the longest length possible, was obtained.

14. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sloma as applied to the claims above, and further in view of Scalice et al. (US Patent 5,587,287) in view of Odawara et al. (US Patent 5,989,819).

Claims 9-11 depend from claim 1 and add the further limitation that an inhibitor is used which inhibits the polypeptide having RT activity. Furthermore, this inhibitor is an antibody or antibody fragment which can be polyclonal or monoclonal.

Sloma does not teach the use of an inhibitor of RT activity.

Scalice et al. teaches that "antibodies which are specific to a thermostable DNA polymerase can be used to reduce or eliminate the formation of non-specific products in polymerase chain reaction methods." (Abstract.)

Scalice et al. does not teach the inhibition of reverse transcriptase.

Odawara et al. teaches an antibody having the ability to inhibit the activity of a reverse transcriptase. (Title).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sloma with those of Scalice et al and Odawara et al. This is because Scalice teach that the inhibition of polymerase can increase the processivity during PCR because it reduces the formation of non-specific products. It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute RT for polymerase, as it was well known in the art that many polymerases have RT activity, and that they too would have been inhibited by an antibody. Furthermore, inhibiting RT activity would have had the same advantageous effect upon the synthesis of cDNA as the inhibition of DNA polymerase would have had upon the DNA of Scalice et al. Also, it was well known in the art that antibodies would have been capable of inhibiting synthesis by RT enzymes, as the teachings of Odawara et al. show.

15. Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sloma as applied to the claims above, and further in view of Ranu (US Patent 5,824,875).

The claims are drawn to the method of claim 2 with the further limitation that a primer is used which has high specificity, and is from a length of 20 bases to 60 bases.

Sloma does not teach the use of a primer from 20 to 60 bases long.

Ranu teach the use of a 50-mer primer as the antisense oligonucleotide in the synthesis of cDNA from mRNA. (Col. 15, lines 40-45).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the primer of Sloma with that of the 50-mer of Ranu. This is

because it was well known in the art at the time of the invention that primers of many different lengths were readily useable to prime the synthesis of mRNA. Furthermore, it was also well known that the longer the primer, the higher the specificity of the priming. Therefore, one of ordinary skill in the art would have been motivated to use a long primer in the synthesis of cDNA. This is because it would have conferred a higher degree of accuracy in the product, allowing for a longer length product if that primer were directed toward the poly A tail.

16. Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sloma as applied to the claims above, and further in view of Vlasuk et al. (US Patent 6,096,877).

The claims are drawn to the methods of claims 15 and 16, with the further limitation that ribonuclease digestion is used, and specifically that the ribonuclease is RNase A or RNase I.

Sloma does not teach the use of ribonuclease.

Vlasuk et al. teach "Preferred methods of obtaining double-stranded cDNA from isolated mRNA include synthesizing a single-stranded cDNA on the mRNA template using reverse transcriptase, degrading the RNA hybridized to the cDNA strand using a ribonuclease, and synthesizing a complementary cDNA strand by using a DNA polymerase to give a double-stranded cDNA." (Col. 29, bridging Col. 30).

It would have been obvious to one of ordinary skill in the art to use an RNase like the one described by Vlasuk et al. with the method of Sloma. That is because the methods are essentially the same, that is, a cDNA copy is being synthesized from an

mRNA. Furthermore, it was well known that RNase was an excellent way to eliminate the mRNA and allow for the creation of a secondary strand of cDNA. Therefore it would have been obvious to use the RNase because it would have eliminated unwanted mRNA from the reaction. Although Vlasuk et al do not specifically teach the use of RNase A or RNase I, it would have been obvious to chose those as they were well known ribonucleases.

***Summary***

Claim 29 is rejected under 35 U.S.C. 112, first paragraph. Claims 5, 7, 13, 16, 18, 19, and 29-30 are rejected under 35 USC 112, second paragraph. Claims 1-6, 15-16, and 21-30 are rejected under 35 USC 102(b). Claims 7-14, 17-20 are rejected under 35 USC 103(a). No claims are free of the prior art.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Any inquiries of a general nature relating to this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 305-3014 or

305-4227. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor

August 17, 2000

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

8/28/00